UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,128	01/02/2002	Fang Liao	11245/46902	8763

26646 7590 08/24/2004

KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,128	LIAO ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *8,9 and 13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Liao *et al.*

Date of priority: 03/31/2000

Election/Restrictions

The response filed on 05/13/04 to the restriction requirement of 11/10/2003 has been received. Applicant has elected Group I, claims 1-7, and 10-12 (as specifically drawn to an antibody that binds to a site on a VE-cadherin, said site being within the about 15 N-terminal amino acids of domain 1 of a VE-cadherin including insertions, deletions or substitutions of from 1 to about 5 amino acids relative to a native VE-cadherin amino acid sequence) for examination with traverse.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Upon review and reconsideration, Groups I-IV are effectively rejoined.

Claims 8-9, 13-22 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Thus, claims 1-7, and 10-12 are pending and are currently under examination.

Specification

The specification is objected to on page 9, line 17 for not supplying the accession number.

Figure 8 and its description (page 7, lines 11+) are objected to for missing information. Specifically, several monoclonal antibodies are labeled with asterisks (i.e. 2G7*)- but there is nothing to indicate what these asterisks symbolize. Clarification is requested. Applicants are reminded that no new matter can be introduced.

Figures 2 and 9 are objected for reciting amino acid sequences (i.e. mNC, mEC, hVEC, mVEC, etc.) in the absence of appropriate sequence identifiers i.e. a SEQ ID NOs:. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

The specification is further objected to for reciting "10G4" on page 23, line 21. Specifically, the specification notes that the 10G4 antibody was also identified as a potent inhibitor of VE-cadherin-mediated adherens junction formation by the in vitro assay criteria and refers to Fig.3. However, Figure 3 does not appear to recite "10G4". Clarification or corrections are requested.

Claim Objections

Claim 12 is objected to for referring to non-elected claims. Specifically, the claims refer to any one of "Claims 1-11". Appropriate corrections are requested.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, and 12 as written, do not sufficiently distinguish over antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, Claim 1 recites "within the about 15 N-terminal amino acids of domain 1". What 15 N-terminal amino acids? Do you mean

amino acids 1-15 of domain 1 or some other fifteen amino acids in or around the N-terminus? As written, there is no frame of reference that clearly distinguishes which 15 amino acids of the N-terminus applicants are referring to. Thus, the metes and bounds of the claims cannot be adequately deciphered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to the monoclonal antibody **E4B9.**

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of **the claimed** monoclonal antibodies are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to the hybridoma cell lines producing said monoclonal antibodies, it would not be possible to practice the claimed invention. Therefore, suitable deposits for patent purposes are required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces

the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

Furthermore, any future amendment to the specification that discloses cells which produce said monoclonal antibodies (i.e. specifically deposited hybridomas) must make sure that that all of the conditions of 37 CFR sections 1.801 through 1.809 have been met. If the deposits were made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository **is required**. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves these specific matters to the discretion of each State. **Additionally, amendment of the specification to recite the date of the deposit and the complete name and address of the depository is required.**

In view of the above, it would require undue experimentation to reproduce the claimed antibodies. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Claims 1-6, 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody or antibody fragment capable of binding to a site on a VE-cadherin, said site being within the about 15 N-terminal amino acids of domain 1 of a VE-cadherin including insertions, deletions, or substitutions within said site (or antibodies capable of specifically binding to SEQ ID NOs: 1-3) wherein said antibody or said antibody fragment is capable of inhibiting VE-cadherin mediated adherens junction formation in vitro but does not exert any significant or substantial effect on paracellular permeability in vitro.

This includes making and using a wide variety of antibodies that bind to a whole universe of polypeptide fragments with the claimed functional activity.

The specification appears to teach (Figure 8) a variety of antibodies that are specific to the first domain of VE-cadherin (19E6, E4B9, 10G4, 2G7) wherein some of these antibodies also appear to inhibit VE-cadherin mediated adherens junction (via Ca^{2+}-switch Assay) formation *in vitro* in the absence of any significant or substantial effect on

paracellular permeability (table 2, page 25; table 3, page 26) such as E4B9, 9D9, and 2G7.

However, the specification has not taught how to make any of these specific antibodies nor has the specification provided any sort of nexus between the disclosed SEQ ID NOs: and any particular monoclonal antibody with the *claimed* functional limitations. Thus, even though applicant's have disclose specific peptide regions, it is not clear if antibodies to this region provide for the functional limitations as to that which is claimed. Further, the state of the art does not recognize nor teach any antibodies specific to domain 1 of VE-cadherin with the claimed functional limitations. For example Corada *et al.* (PNAS, Vol. 96, pages 9815-9820, 1999, IDS) teach a monoclonal antibody (BV13) specific for the extracellular domain of VE-Cadherin (amino acids 1-486) that would appear to encompass antibodies that bind domain 1 of VE-Cadherin (including insertions, deletions or substitutions of domain 1) in which BV13 increased vascular permeability (abstract, materials & methods). Similarly, Corada *et al.* (Blood, Vol. 97, No. 6, March 2001) teach a monoclonal antibody (Cad 5) that binds to domain 1 (EC1) of VE-cadherin that appears to have substantial effects on paracellular permeability (page 1683, Table 1). Further, the specification identifies other monoclonal antibodies 10G4 and 19E6 that are specific to EC1 of VE-cadherin in the absence of the claimed functional characteristics (tables 2 and 3). Further, the specification does not disclose sufficient guidance and objective evidence as to the linear and or three-dimensional conformation of the amino acids which constitute the epitopes recognized by the claimed invention. Assertion of an epitopes's proximity within an antigen (i.e. about the 15 N-terminal amino acids) does not provide sufficient guidance to one of relative skill in the

art to make and or use the presently claimed invention. Antibodies bind to structural shapes that may be linear stretches of amino acids, conformational determinants formed by the folding of peptides, carbohydrate moieties, phosphate or lipid residues or a combination thereof. Moreover, as evidenced by Greenspan et al., defining epitopes is not as easy as it seems (Nature Biotechnology 7:936-937 (1999). Even when the epitope is defined, in terms of the spatial organization of residues making contact with ligand, then a structural characterization of the molecular interface for binding is necessary to define the boundaries of the epitope (page 937, 2nd column). Since the specification has not identified which amino acids are critical or essential characteristics of the epitope, it would not be predictable, to one of relative skill in the art, to isolate an antibody specific for any and all epitopes (including substitutions, deletions, or insertions) within the about 15 N-terminal amino acids of domain of VE-cadherin with the claimed functional properties.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make and use any and all such claimed antibodies. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to make and or use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Database IMSDRUGNEWS (R & D Focus Drug News, November 17, 1997).

The cited abstract refers to the highly specific monoclonal antibody antagonist (**E4B9**) of VE-cadherin 2 that is claimed in Claim 7. Absent evidence to the contrary, the cited E4B9 antibody also encompasses the functional limitations as claimed in Claims 1-6.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN

Gary B Nickol

GARY NICKOL
PRIMARY EXAMINER